

by causing disturbances to cellular carbohydrate metabolism at critical periods during development. Further, I have experimental proof that insulin-induced deformities can be prevented to a remarkable extent by injecting nicotinamide and riboflavin into eggs along with insulin, and details of this work will be given in another paper dealing with the preventive aspect of the problem.

### Summary

Though genetic factors play an important part in the causation of congenital anomalies, it has been shown in recent years that certain environmental factors can interfere with the normal developmental processes in the embryo.

An account of the skeletal abnormalities induced by insulin has been given.

It has been suggested that unchecked insulin hypoglycaemia during the early stages of development may adversely affect the development of the cartilaginous skeleton and of the eyes by depriving them of their essential constituent mucoprotein to varying degrees.

This experimental research has been conducted in the Department of Orthopaedic Surgery, University of Liverpool, with the aid of a scholarship granted by the Government of India till October, 1949, and thereafter with a Fellowship awarded by the University of Liverpool, and my grateful acknowledgments are extended to them. I wish to thank Mr. Bryan McFarland, director of orthopaedic studies, and his assistant, Mr. G. V. Osborne, for providing the facilities for carrying out this research; Sir Edward and Lady Mellanby for their helpful criticism; Dr. C. A. St. Hill and Miss M. Lichfield for the histological sections; Mr. W. Lee for the photographs and photomicrographs; Miss B. Duckworth for the drawing; and Burroughs Wellcome Ltd. for a supply of crystalline insulin.

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The booklet *Notes on the Diagnosis of Occupational Diseases Prescribed under the National Insurance (Industrial Injuries) Act* is now obtainable by medical practitioners from H.M.S.O. or through any bookseller for 1s. 6d. An earlier edition was issued in 1948 to those medical practitioners to whom claimants to industrial insurance benefit on account of prescribed occupational diseases were being referred for initial diagnosis. Notes on pneumoconiosis and byssinosis have now been added to the booklet.

## MORTALITY FROM AND RISK OF GASTRIC CARCINOMA AMONG PATIENTS WITH PERNICIOUS ANAEMIA\*

BY

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AND

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The introduction of concentrated preparations of liver and stomach in the treatment of pernicious anaemia (Minot and Murphy, 1926) has changed completely the prognosis of this complaint. The disease, which previously had followed a capricious but usually rapidly fatal course, could now be kept under control, so that as a rule the patients enjoyed a long period of freedom from symptoms with full working capacity.

It is now possible, with more than 20 years' experience of this treatment, to evaluate the prognosis of the disease under the radically altered conditions. While studying for a different purpose a group of patients suffering from pernicious anaemia we arrived at results which differ in several respects from those previously reported and which we therefore feel justified in publishing.

### Present Investigations

The series comprises a fairly large number of patients treated for pernicious anaemia at the Bispebjerg Hospital, Medical Department B, during the period 1928 to 1949. A few foreigners and provincials have been omitted. All the case records were reviewed and the diagnoses confirmed according to the following criteria: a characteristic clinical picture, typical blood findings (megalocytic, hyperchromic anaemia, anisocytosis, leucopenia, increase in reticulocytes following specific therapy), and achlorhydria refractory to histamine.

In cases in which the diagnosis had been made before admission to hospital, data regarding the earliest clinical

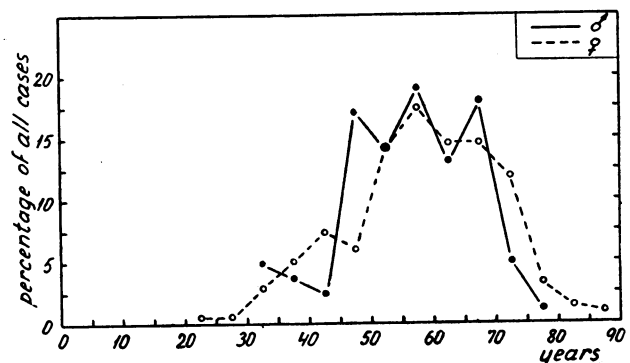


FIG. 1.—Age distribution of 219 females and 82 males suffering from pernicious anaemia. (Age when the disease was diagnosed.)

symptoms and blood findings were sought for confirmation. It was decided to leave out one case of megalocytic anaemia in a pregnant woman and two cases in which specific treatment was suspended at the recommendation of the department, since the blood findings were atypical;

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one of them has been symptom-free without treatment for 2½ years, but contact with the other has been lost.

Thus curtailed, the series comprises 301 patients—219 females (72.7%) and 82 males (27.3%). Fig. 1 shows the age of the patients when the diagnosis was made (average: females 59.1, males 56.4 years).

Table I groups the series according to the length of the follow-up period, and gives the number of deceased patients within each group.

TABLE I.—Follow-up Period in 301 Cases of Pernicious Anaemia

Follow-up Period (Years)	Females		Males	
	Cases	Deaths	Cases	Deaths
1-5 .. ..	45	32	24	12
6-10 .. ..	72	26	22	9
11-15 .. ..	51	16	17	5
16-20 .. ..	39	7	13	5
21-25 .. ..	12	2	6	1
Total .. ..	219	83	82	32

**Mortality Among Pernicious Anaemia Patients**

The average follow-up period was 10.5 years (10.3 years for males and 10.7 for females), the study being concluded on June 1, 1949. By that time 83 of the 219 females and 32 of the 82 males had died.

On the basis of the mortality among the population of Copenhagen during the period 1935-9, it would be expected that, of 301 individuals of the same age and sex distribution and followed up for the same length of time as the patients with pernicious anaemia, 89 females and 28 males would die. It is evident from Table II that the actual findings are in perfect accordance with the expected deaths, and that in the present series the mortality did not exceed what is normal.

TABLE II.—Deaths Among 301 Patients with Pernicious Anaemia as Compared with the Number of Deaths Among a Corresponding Group of Normal Persons

	No. of Deaths Among 301 Patients with Pernicious Anaemia	Expected No. of Deaths
Females .. ..	83	89
Males .. ..	32	28
Total .. ..	115	117

**Prognosis**

For the purpose of adjudging the actual prognosis in cases of pernicious anaemia the authors chose a follow-up period of 10 years, including in this group only those patients whose disease was diagnosed prior to 1940. This group comprises 222 patients (168 females and 54 males). A total of 51 females and 17 males died during the follow-up period. On the basis of the ordinary mortality it was calculated that, among a population of the same age and sex distribution as the 222 patients, 50 females and 13 males would be expected to die in the course of 10 years.

Figs. 2 and 3 show the survivors among the females and males, respectively, with pernicious anaemia followed up for a minimum of 10 years, and also the survivors among a population of the same age and sex distribution. It is clear from the diagrams that, so far as the females are concerned, the mortality of patients with treated pernicious anaemia is the same as that of the average population. The apparently high mortality among the males (Fig. 3) proves, upon statistical calculation, to be within the error of the mean, due perhaps to chance in this small series

of males. In other words, in the present series the life expectancy among the female patients is the same as among normal females; in the case of the males there is a slightly higher, but not significantly excessive, mortality.

In contrast to these findings, Jørgensen (1949), in his series of 148 females and 58 males suffering from pernicious anaemia, found the mortality in the females to be 13% and in the males 107% above the normal. He is of the opinion that this high mortality is due entirely to inadequate treatment. The difference in his mortality rate from that of the present series may be due to the fact that our patients were treated largely with the same preparation ("exopylorin," medicinalco), whereas Jørgensen's patients had undergone various treatments. In addition, a large number of our patients have been examined at intervals for years because of the particular interest devoted to pernicious anaemia in the department.

**Causes of Death among Pernicious Anaemia Patients**

Up to June 1, 1949, 115 (83 females and 32 males) out of the 301 patients had died. Table III shows the way in which the causes of death were ascertained.

TABLE III.—Sources of the Cause of Death in 115 Cases of Pernicious Anaemia

	Cause of Death Confirmed by		
	Case Record and Necropsy	Case Record Without Necropsy	Death Certificate
Females .. ..	13	36	34
Males .. ..	7	12	13
Total .. ..	20	48	47

Sixty-eight patients (49 females and 19 males) died in hospital. In the case of 13 females and 7 males the cause of death was confirmed by necropsy. Forty-seven patients died in their homes, and the cause of death was derived from the death certificates. In cases in which the latter mentioned carcinoma, further details regarding the diagnosis were obtained from the family doctor or the hospital department concerned.

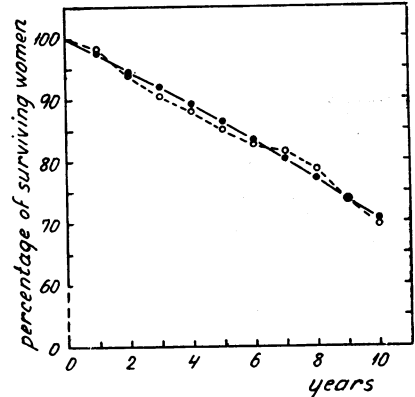


FIG. 2.—Percentage of survivors among 168 females suffering from pernicious anaemia (O--O) as compared with the calculated mortality among a corresponding population (●--●).

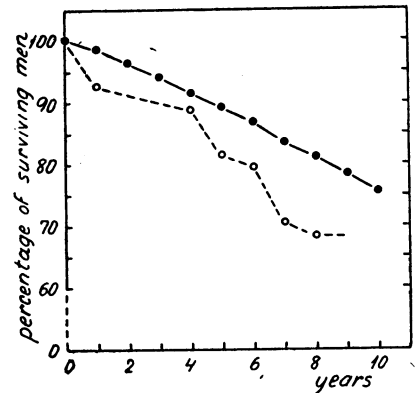


FIG. 3.—Percentage of survivors among 54 males suffering from pernicious anaemia (O--O) as compared with the calculated mortality among a corresponding population (●--●).

TABLE IV.—Causes of Death in 115 Cases of Pernicious Anaemia

	Females	Males	Total
Pernicious anaemia	2	1	3 (3%)
Carcinoma of stomach	8	6	14
"    "    liver	1		1
"    "    colon	1		1
"    "    uterine cervix	1		1
"    "    thyroid gland	1		1
"    "    mammary gland	1		1
"    "    prostate		2	2
Heart disease	23	9	32 (28%)
Pulmonary diseases (apart from cancer)	13	7	20 (17%)
Cerebral disorders (apart from tumours)	19	5	24 (21%)
Pyelonephritis	5		5
Uræmia		1	1
Papilloma of urinary bladder		1	1
Intestinal obstruction	2		2
Peritonitis	1		1
Cholangitis	1		1
Cirrhosis of liver	2		2
Ovarian cystoma	1		1
Agranulocytosis (due to drugs)	1		1
<b>Total</b>	<b>83</b>	<b>32</b>	<b>115</b>

The causes of death in the 115 cases of pernicious anaemia are listed in Table IV. Pernicious anaemia appears to have been the immediate cause of death in only the three cases given. Two of these patients were senile females who were admitted to hospital in a state of severe anaemia, and both were so debilitated that adequate therapy proved of no avail. The third patient refused treatment, and died in his home from severe anaemia a fortnight after discharge from hospital.

In this connexion it might be interesting to call attention to a study from the Simpson Memorial Institute published by Sturgis (1939). Analysing the causes of death in 150 cases of treated pernicious anaemia dying within the first 10 years after the introduction of liver therapy, he arrived at the result that half the patients died from anaemia (particularly myelopathic manifestations with sphincter disturbances) and the other half from irrelevant causes. In the present series myelopathic symptoms did not constitute the cause of death in any case.

**Gastric Carcinoma in Pernicious Anaemia Patients**

Thirteen females and eight males died from carcinoma (Table IV). On the basis of the mortality from carcinoma among the population of Copenhagen, 1935-9, it may be calculated that, among 301 individuals of the same age and sex distribution and followed up for the same length of time as the anaemic subjects, 6 males and 15 females would be expected to die from carcinoma (Table V). In

TABLE V.—Number of Deaths From Carcinoma Among the Series of 301 Cases of Pernicious Anaemia as compared with the Number of Expected Cancer Deaths

	No. of Patients	Deaths from Cancer	
		Actual	Expected
Females	219	13	15
Males	82	8	6
<b>Total</b>	<b>301</b>	<b>21</b>	<b>21</b>

other words, the mortality from carcinoma among the present series was not excessive.

It is striking that no fewer than 8 out of 83 females (10%) and 6 out of 32 males (19%) died from carcinoma of the stomach. In addition, the series includes a man who underwent operation for gastric carcinoma and who six months later is still surviving in a debilitated state. Details of the 15 cases of gastric carcinoma are given in Table VI.

Of the females, four died in hospital and were examined at necropsy, but microscopical examination was performed

TABLE VI.—Fifteen Cases of Gastric Carcinoma Occurring Among 301 Patients Suffering From Pernicious Anaemia

Case	Sex and Age	Duration of Pernicious Anaemia Before Gastric Carcinoma was Diagnosed (Years)	Site of Tumour in Stomach	Microscopical Examination
1	F 60	3	Ulcerated tumour occupying entire pyloric area (necropsy)	Papilliferous carcinoma
2	F 71	1	Large tumour occupying distal half of stomach (x-ray)	Not performed
3	F 72	2	Flat tumour, size of child's hand, on posterior wall of stomach, 6-7 cm. from pylorus (necropsy)	" "
4	F 72	1	Firm and nodular tumour, size of goose's egg, occupying entire pyloric antrum (necropsy)	" "
5	F 75	15	Entire pyloric area tapers into fine irregular canal (tumour of pylorus) (x-ray)	" "
6	F 58	9	Irregular, large filling defects on middle of lesser curvature, reaching to and involving entire cardia (x-ray)	" "
7	F 68	17	From fundus a large irregular filling defect extends 8-10 cm. into body (x-ray, operation)	" "
8	F 68	4	Ulcerating carcinoma, size of an orange, on middle of lesser curvature (necropsy)	" "
9	M 48	19	Nodular tumour, size of closed fist, on middle of lesser curvature (operation)	Adenocarcinoma
10	M 66	13	Circular carcinoma, size of closed fist, in area of pyloric antrum (operation)	Adenocarcinoma with solid areas
11	M 68	8	Diffuse infiltration of entire stomach (necropsy)	Solid, scirrhus, diffuse carcinoma
12	M 70	7	Firm tumour, size of half-crown, on middle of greater curvature (necropsy)	Adenocarcinoma
13	M 57	5	X-ray: pyloric tumour. Operation revealed cicatricial stenosis. Five years later entire stomach was involved in diffuse scirrhus infiltration (operation and x-ray)	Not performed
14	M 61	7	Circular constriction of middle area of body which shows irregular, sharp contours. Fundus and pylorus normal (x-ray)	" "
15	M 57	14	Operation revealed an ulcerated tumour, size of palm of hand	Adenocarcinoma

in only one case. Four died in their homes, the diagnoses having been confirmed by characteristic x-ray findings, occult bleeding, and the clinical course of the disorder. So far as the males are concerned, histological verification was available from operation or necropsy specimens in five cases. In two cases the diagnoses were substantiated by typical x-ray findings. The age stated in the table refers to the age when the diagnosis of carcinoma was made, and, since the patients usually die from carcinoma within the first year (the longest interval in this series being 18 months), the age at diagnosis accords fairly well with the age at death.

All the patients were examined radiologically. Five (one female and four males) underwent operations; necropsy was performed in six instances (four females and two males).

On the average, pernicious anaemia was of eight years' standing (seven years for females and ten years for males) when gastric carcinoma was diagnosed, the average age when the carcinoma was diagnosed being 68 years for the eight females and 61 years for the seven males. This difference in age is not statistically significant, but in all probability it is real, since Jørgensen found a corresponding sex difference in his series.

On the basis of the ordinary mortality from gastric carcinoma among the population, corresponding as regards sex and age to the 301 cases of pernicious anaemia and followed up for the same length of time, it may be calculated that 3.5 females and 1.7 males should have died from

TABLE VII.—Incidence of Gastric Carcinoma Among 301 Cases of Pernicious Anaemia as Compared with the Expected Incidence in a Corresponding Normal Population

	No. of Patients	Cases of Gastric Carcinoma	
		Occurring	Expected
Females ..	219	8 (4%)	3.5 (1.6%)
Males ..	82	7 (9%)	1.7 (2.1%)
Total ..	301	15 (5%)	5.2 (1.7%)

gastric carcinoma at the end of the follow-up period. Table VII gives the cases of gastric carcinoma occurring in the present series as compared with the expected incidence.

The number of patients dying from gastric carcinoma in the present series has thus far exceeded the expected deaths. The difference is significant for females as well as for males. It strikes one that the increased incidence of gastric carcinoma does not involve a corresponding increase in the incidence of total carcinoma.

Previous workers (Jenner, 1939; Waldenström, 1945; Kaplan and Rigler, 1945, 1947; Bourne, 1948) have called attention to the particular predisposition to gastric carcinoma among patients suffering from pernicious anaemia. This finding was recently confirmed by Jørgensen, who emphasized that the increase in the incidence of gastric carcinoma among patients suffering from pernicious anaemia was more marked among males than among females, an observation which accords with the findings in the present series. It is difficult to explain this male preponderance. The data available in our series afforded no evidence that the male patients developing gastric carcinoma were alcohol addicts.

Attempts have been made to explain the high incidence of gastric carcinoma in association with pernicious anaemia as being the result of the pathological changes found in the stomach in the latter condition. It has been pointed out by Meulengracht (1939) that patients with pernicious anaemia are affected with atrophic gastritis, localized primarily to the fundal area, whereas the mucosa of the distal part of the stomach is comparatively intact. If this gastritis were the precursor of gastric carcinoma, such carcinoma would be expected to develop by preference in the fundal area or at least in the proximal part of the body.

According to Torgersen (1944) gastric carcinoma in pernicious anaemia is in the great majority of cases localized to the fundus and to the proximal part of the body. In contrast, gastric carcinoma in a non-selected material was found to be situated in the pylorus and pyloric antrum in 50 to 60% of the cases. Torgersen's series comprises 106 cases of pernicious anaemia coexisting with gastric carcinoma (90 from the literature and 16 of his own). According to the description, in only two of his own cases was the carcinoma unmistakably in the fundus, whereas in seven it was in the body and in seven in the pylorus.

There seems to be some incongruity between Torgersen's observations in his own cases and the conclusion which he claims to be able to draw from earlier reports. The earlier reports of gastric carcinoma in association with pernicious anaemia have usually been of single cases or of groups comprising only a few patients. Among a somewhat larger series (Table VIII), the one reported by Strandell and Jansson (1937) is worth mentioning. Among 686 cases of pernicious anaemia they found 21 of gastric carcinoma in the following sites: nine in the pylorus, four in the fundus, and eight in the body of the stomach.

TABLE VIII.—Site of Gastric Carcinoma Occurring in 85 Cases of Pernicious Anaemia

	Pylorus and Antrum	Body	Fundus	Diffuse
Jenner (1939) ..	3	2	1	1
Strandell and Jansson (1937)	9	8	4	
Washburn and Rozendaal (1938) ..	4	2	3	
Torgersen (1944) ..	7	7	2	
Doehring and Eusterman (1942) ..	8	4	3	2
Present series ..	5	6	2	2
Total ..	36	29	15	5

Among 906 cases of pernicious anaemia Washburn and Rozendaal (1938) found gastric carcinoma in nine—three were in the fundus, two in the body, and four in the pylorus.

Jenner (1939), studying 181 cases of pernicious anaemia, found among them seven cases of gastric carcinoma. In one case the fundal area was definitely the site of the tumour; in two cases the site was probably the body; in three it was natural to interpret the tumour as being in the pylorus; and in the last case the growth was without doubt a scirrhus involving the entire stomach.

Doehring and Eusterman (1942) found 17 instances of gastric carcinoma among 1,014 patients suffering from pernicious anaemia. Eight were situated in the distal third of the stomach, four in the middle third, and three in the proximal third; two cases involved the entire stomach. These authors concluded that the site of gastric carcinoma in patients suffering from pernicious anaemia did not differ from that found normally.

The reported cases of gastric carcinoma in the presence of pernicious anaemia therefore fail to afford evidence that the growths in these patients are situated by preference in the fundal area or in the proximal part of the body.

The present series includes five cases of pyloric carcinoma, six of the body, and two of the fundus; in two instances the entire stomach was involved. Accordingly, this group does not confirm the theory that gastric carcinoma in the presence of pernicious anaemia should be localized by preference to the fundus.

The reason for the particular predisposition to gastric carcinoma among patients suffering from pernicious anaemia remains unelucidated. Possibly the explanation is that both pernicious anaemia and gastric carcinoma result from achlorhydria. If so, it is not unnatural that the two conditions should at times coexist. There is perhaps a question of inherited factors, since achlorhydria, an almost invariable sign of both lesions, occurs with particular frequency in families affected with pernicious anaemia.

A wide study of the familial occurrence of achlorhydria, pernicious anaemia, and gastric carcinoma may help in elucidating the relationship between these lesions. Investigations along these lines are being carried out.

### Summary

A total of 219 females and 82 males who received treatment for pernicious anaemia at the Bispebjerg Hospital, Medical Department B, Copenhagen, during the period January, 1928, to June, 1949, have been studied. Of these, 83 females and 32 males have died. The expected number of deaths is 89 females and 28 males.

Two hundred and twenty-two patients have been followed up for more than ten years. Female patients with pernicious anaemia have the same chances of survival as normal females, whereas there is a slightly but not significantly higher mortality among the males.

The causes of death are tabulated. Twenty-one patients died from carcinoma, a figure which corresponds to the expected number of cancer deaths. Among this group, however, no fewer than eight females and six males died from gastric carcinoma. The expected number of deaths from carcinoma in all sites is 15, from gastric carcinoma only 5, so that the excessive mortality from gastric carcinoma is statistically significant.

It is found that patients suffering from pernicious anaemia do not develop their gastric carcinoma in the fundus and upper part of the body of the stomach, where the pathological changes characteristic of pernicious anaemia are localized. Possibly the explanation is that both pernicious anaemia and gastric carcinoma result from achlorhydria.

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## HAEMOLYTIC STREPTOCOCCAL GANGRENE OF BREAST SUCCESSFULLY TREATED WITH STREPTOMYCIN

BY

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Haemolytic streptococcal gangrene was first accurately described by Meleney (1924). In almost all cases there is an initial lesion which may escape the patient's notice. The limbs are affected more commonly than any other part of the body, as they are exposed to injury. The disease may occur in the scrotum (Marcus, 1949) and rarely on the trunk. Its clinical course is characterized by very rapid development. Within twenty-four hours the affected part becomes markedly swollen and shows all the signs of a rapidly spreading inflammation. In a day or two blisters and bullae begin to form and then the skin becomes frankly gangrenous. The condition is due to the haemolytic streptococcus, which can be obtained by culturing the discharge aerobically or anaerobically. Other organisms, such as *Staphylococcus aureus*, *Pseudomonas pyocyanea*, *Bact. coli*, *Proteus vulgaris*, *Streptococcus faecalis*, and diphtheroids may occur as secondary invaders.

Meleney (1924) recommends incision as far as the extension of the subcutaneous necrosis, but not further, as incisions in the zone of cellulitis may be harmful. The gangrenous skin should be excised as soon as the line of demarcation has developed and removal can be adopted without causing much bleeding. Amputation is rarely necessary, as the infection is superficial in most cases and can usually be combated by superficial incisions.

Penicillin and the sulphonamides have proved of value in haemolytic streptococcal infections, and in many cases render incisions unnecessary. The following two cases may be of interest, as these drugs failed to prevent the infection spreading, but when used with streptomycin localization occurred within a few hours.

## Case 1

A married woman aged 57 was admitted for investigation for Cushing's syndrome. She had a small infected area on the left breast, for which she was given 100,000 units of penicillin daily. The inflammation extended by 1½ in. (3.8 cm.) in 24 hours and discharged copiously. When seen five days later the skin of the breast, except for the nipple and areola, was gangrenous (Fig. 1). The spreading margin extended upwards towards the clavicle, and was painful and vesiculated. Sulphatriad, 1 g. thrice daily, was given for 48 hours.

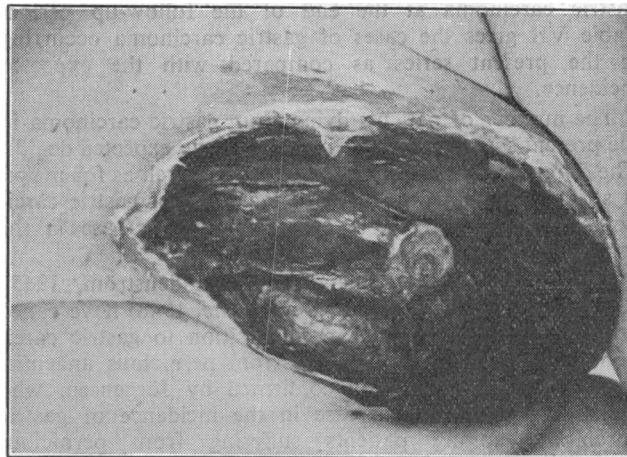


FIG. 1.—Case 1. Before streptomycin. The skin of the breast is gangrenous, and the gangrenous process is extending by 1½ in. daily.

Culture on February 16 showed: haemolytic streptococcus sensitive to 1/16 unit of penicillin per ml. and 8 units of streptomycin per ml.; *Staph. aureus* sensitive to 32 units of penicillin per ml. and 2 units of streptomycin per ml. Streptomycin, 0.5 g. six-hourly, was given—total 6 g.

The general condition improved within 12 hours. The tenderness was lessened, the spreading process was arrested, and the gangrenous skin showed a line of demarcation. Culture: haemolytic streptococci sensitive to 1/16 unit of penicillin per ml. and 8 units of streptomycin per ml.; *Staph. aureus* resistant to at least 32 units of penicillin per ml. and sensitive to 4 units of streptomycin per ml.

On February 18 the bacteriological findings and sensitivity to penicillin and streptomycin were unaltered. About three-quarters of the gangrenous skin had separated, and this was easily cut away with scissors, leaving a remarkably clean granulating surface. The remainder of the skin was removed next day without causing much bleeding; the nipple and areola were left intact. A small area below the nipple was affected more deeply than the remainder of the breast and contained a slough about ¼ in. (1.9 cm.) long. Culture from this region grew *Proteus vulgaris*.

On February 23 healing began, and granulations were healthy except for a small area below the nipple. Culture from this region grew *Proteus vulgaris* resistant to at least 32 units of penicillin. On March 23 postage-stamp Thiersch grafts were applied to the granulating surface. By April 1 most of the grafts had taken successfully and healing proceeded rapidly. The raw area had completely epithelized by April 18.

## Comment on Case 1

The haemolytic streptococcus isolated was of Lancefield Group A. It was not completely eliminated from the margin of the gangrenous area during the period streptomycin was given. After the gangrenous skin had been removed the organisms were not found in repeated cultures from the margin of the granulating tissue. As the skin was not viable when streptomycin treatment was initiated